Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarket Adverse Event Review

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Product Name(s):	Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium)
Pediatric Exclusivity Approval Date:	September 24, 2010
Application Type/Number:	NDA 22-532
Applicant/Sponsor:	Bayer Healthcare Pharmaceuticals, Inc.
OSE RCM #:	2012-834

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EXECUTIVE SUMMARY

Review of Postmarketing Adverse Event Reports to FDA

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV 1) was asked to summarize post-marketing reports of adverse events associated with the use of Beyaz [ethinyl estradiol (EE), drospirenone (DRSP), levomefolate calcium] in pediatric patients (0-17 years of age). The main focus of the pharmacovigilance review was to evaluate pediatric deaths and pediatric reports of serious unlabeled adverse events with Beyaz.

Beyaz is the first combination oral contraceptive (COC) to contain *levomefolate calcium* and is indicated for use by women to prevent pregnancy.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the "data lock" date of May 1, 2012. AERS contained 467 reports for Beyaz. Pediatric reports represent approximately 4% of the total (19 reports/467 reports). There were no pediatric deaths.

Of note, there were 6 cases of thromboembolic events including one report of retinal thromboembolism and three reports of pulmonary embolism. Thromboembolic events are serious labeled adverse events that may occur with COC use. The Warnings section of Beyaz was recently updated and contains language stating that COCs containing drospirenone may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Additionally, a description of epidemiological data regarding the risk of thromboembolism with drospirenone-containing COCs is provided below.

Overall, this postmarketing evaluation found no unexpected evidence of pediatric safety concerns with Beyaz. DPV 1 will continue pharmacovigilance activities associated with Beyaz.

Safety of Combined Oral Contraceptives Containing the Progestin Drospirenone - Epidemiological Evidence

Although there are currently no epidemiologic studies evaluating the safety of Beyaz specifically, Beyaz contains the progestin drospirenone and several epidemiologic studies of drospirenone safety have been published since the approval of the first drospirenone-containing oral contraceptive in 2001. These epidemiologic studies and the safety of drospirenone were discussed at the Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 8, 2011. These studies evaluated the risk of thrombotic and thromboembolic events. The studies reviewed did not provide consistent estimates of the comparative risk of VTE nor did they account for important known and unknown patient characteristics that could influence prescribing and likely affect the risk. It remains unclear whether the increased VTE risk seen in some of the epidemiologic studies is actually due to use of drospirenone-containing COCs, or due to underlying conditions of the patients to whom these products are prescribed.

Some of these studies have evaluated the risk for VTE among women as young as 10 years of age. Two studies have shown that the relative risk of a thromboembolic event associated with drospirenone-containing products was greater for women younger than 30 or 35 years of age than for older women. Younger women report using drospirenone-containing products for contraceptive and non-contraceptive reasons, results that are consistent with the observations of the AERS case series for Beyaz.

DEPI-II continues to explore ways to better understand the possible increased VTE risk associated with all drospirenone-containing products, including Beyaz, in women of all ages.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Beyaz [drospirenone (DRSP), ethinyl estradiol (EE), and levomefolate calcium tablets] is the first combination oral contraceptive (COC) indicated for use by women to prevent pregnancy to contain *levomefolate calcium*. Each Beyaz blister pack contains 28 tablets arranged in the following order: 24 pink tablets each containing 3 mg DRSP and 0.02 mg EE, and 4 light orange tablets each containing 0.451 mg levomefolate calcium. DRSP is a spironolactone analogue with progestational, antimineralcorticoid, and antiandrogenic activity. Both DRSP and EE are available in the approved COC products Yaz and Yasmin, as well as generic versions of these products.

1.2 PEDIATRIC FILING HISTORY

Per pediatric legislative initiatives, the following pediatric indications were studied:

1) prevention of pregnancy
2) treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception
3) treat moderate acne for women at least 14-years-old who have achieved menarche and desire on oral contraceptive for birth control
4) to raise folate levels in women who choose to use an oral contraceptive for contraception.

1.3 PEDIATRIC LABELING

The labeling for Beyaz has the following information concerning the pediatric population:

Pediatric Use
Safety and efficacy of Beyaz has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

1.4 RECENT ADVISORY COMMITTEE MEETINGS

On December 8, 2011 a Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held to discuss the benefits and risks of drospirenone (DRSP)-containing COCs in light of the emerging safety concern that the risk of venous thromboembolism (VTE) associated with use of these products may be higher when compared to oral contraceptives that contain other progestins, including levonorgestrel. As mentioned above, Beyaz is a DRSP-containing COC product. A synopsis of the epidemiologic study results discussed at this Joint Meeting and other publications relevant to use in adolescents is presented in Section 4.3.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1 (see Appendix A).

Table 1. AERS Search Strategy*	
Date of search	May 1, 2012
Time period of search	September 24, 2010^ - May 1, 2012
Product Terms	Beyaz

* See Appendix B for description of the AERS database.
^ Approval date of pediatric labeling

3 RESULTS

3.1 AERS REPORTS

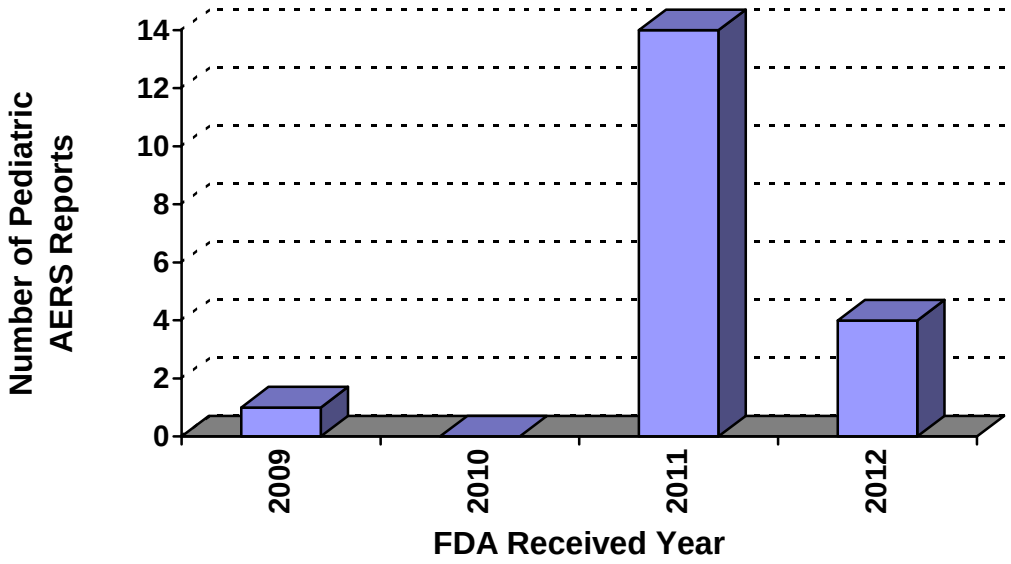
Table 2 summarizes the total number of *domestic* AERS reports. The AERS search did not retrieve any *foreign* reports.

Table 2. Total number of *domestic* AERS reports* (September 24, 2010 - May 1, 2012)			
	All reports	**Serious‡**	**Death**
Adults (≥18 years)	158	75	4
Pediatrics (0-17 years)	19	9†	0
Age unknown (null values)	290	46	1†
Total	467	130	5

* May include duplicates and have not been assessed for causality
‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
† Insufficient clinical information to determine age; also see Figure 2

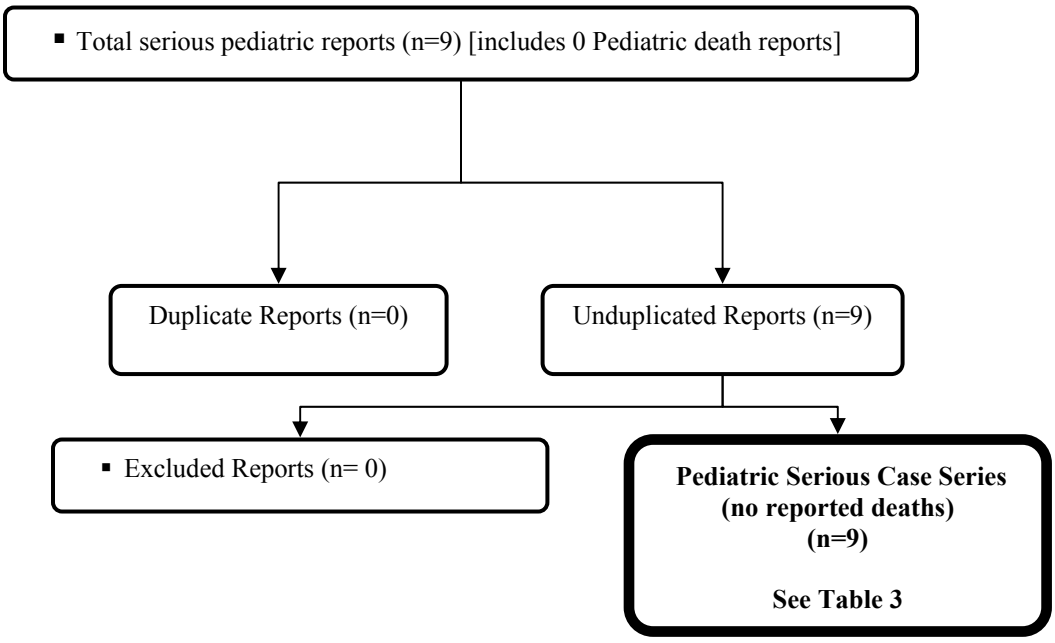
3.2 FIGURE 1. TOTAL NUMBER OF PEDIATRIC REPORTS (INCLUDING SERIOUS AND NON-SERIOUS) FOR BEYAZ, BY YEAR OF FDA RECEIPT (SEPTEMBER 24, 2010 - MAY 1, 2012) (N=19)

These numbers include data where age (0-17 years) is known and may contain duplicate reports. Data for 2012 represents a partial year.



When reviewing pediatric reports with serious outcomes, we were unable to determine whether one report with the age unknown reporting an outcome of death concerned a pediatric patient. **Figure 2** below summarizes the specific selection of cases to be reviewed in **Section 4**.

3.3 FIGURE 2. SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.4 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the 9 AERS cases from the Pediatric Serious Case Series with Beyaz.

Appendix C lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the Pediatric Case Series.

Table 3. Descriptive characteristics of Pediatric Case Series [September 24, 2010 - May 1, 2012]

		(N=9)
Age (n=9)	12-15 years	2
	16-17 years	7
Sex	Female	9
Country of reporter	United States	9
Report type	Expedited	5
	Direct	2
	Periodic	2
Event date	2009, 2010, 2012	0
	2011	5
FDA received date	2009	1
	2010	0
	2011	6
	2012†	2
Indications	Contraception	3
	Menstruation Irregular	1
	Menstrual cycle management	1
	Unknown	4
Serious Outcomes*	Life-threatening and Hospitalized	1
	Hospitalized	3
	Other serious	5

† Partial year

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES AND EPIDEMIOLOGIC STUDIES

A postmarketing assessment of serious pediatric cases (N=9) finds no unexpected changes in the type or severity of adverse events that indicate a clinically significant change in the known safety profile of Beyaz (ethinyl estradiol, drospirenone, levomefolate calcium). These 9 events are summarized in section 4.2.

4.1 SUMMARY OF PEDIATRIC DEATHS (N=0)

There are no pediatric deaths in this pediatric case series.

4.2 SUMMARY OF SELECTED SERIOUS PEDIATRIC ADVERSE EVENTS

4.2.1 Thromboembolic events (n=6)

There were 6 postmarketing cases of thromboembolic events which are labeled events.

In the four reports describing hospitalization, there was one report of retinal thromboembolism and three reports of pulmonary embolism. In each of these four cases, the clinical outcome was unknown or not reported. Similarly, in the two cases not reporting hospitalization (one report each of pulmonary embolism and VTE), the clinical outcome was also unknown or not reported. Confounding factors in these cases include one or more of the following: predisposing medical conditions (e.g., morbid obesity), polypharmacy for both reported and unreported medical conditions, and narratives with insufficient clinical information to assess (also see Appendix D).

Thromboembolic events are serious labeled adverse events that may occur with COC use. The Warnings section of Beyaz was recently updated and contains language stating that COCs containing drospirenone may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Additionally, a description of epidemiological data regarding risk of thromboembolism with drospirenone-containing COCs is provided below in Section 4.3.

4.2.2 Other Miscellaneous Adverse Event

The 3 additional cases include one report each of toxic shock syndrome (TSS), syncopal episodes, and musculoskeletal pain with anxiety. Causality in these three cases can not be determined. All three cases are confounded or had incomplete clinical narratives. The report of TSS occurred in the context of prior TSS and current documented 'strep' infection which is an independent risk factor for TSS (also see Appendix E).

Beyaz is FDA-approved for premenstrual dysphoric disorder (PMDD) which can include musculoskeletal pain and anxiety symptoms. Syncopal episodes and TSS are not labeled adverse events and while insufficient clinical information was provided to assess causality, DPV will continue to monitor for these events.

4.3 CURRENT INFORMATION ON THE SAFETY OF COMBINED ORAL CONTRACEPTVES CONTAINING THE PROGESTIN DROSPIRENONE: EPIDEMIOLOGIC STUDIES

Although the epidemiologic studies conducted to date did not evaluate Beyaz specifically, the safety concerns identified by these epidemiologic studies published since the introduction of COCs containing drospirenone in 2001 were discussed in detail at the December 8, 2011 Joint Meeting of the Reproductive Health Drugs Advisory Committee (AC) and the Drug Safety and Risk Management Advisory Committee. These studies and the FDA's perspectives on them

were summarized in the background package posted for this AC. Section 2 and Appendix 1 of the background document provide more information on most postmarketing epidemiologic studies published through 2011 and include a review of an FDA-funded study. All but one of these studies included only the drospirenone-containing contraceptive with 30 mcg of ethinyl estradiol (EE) rather than the 20 mcg EE in Beyaz. In the one study that assessed VTE risk in the 20 mcg EE product without levomefolate calcium contained in Beyaz, the incidence rate of VTE was similar to that for the 30 mcg EE product.

Other than the studies required by regulatory agencies (Seeger 2007, Dinger 2007), which showed no increased VTE risk, most other epidemiologic studies reported a two- to three-fold increased VTE risk with drospirenone-containing products compared to other progestin-containing products and it is expected that Beyaz would demonstrate a similar safety profile. The studies reviewed did not provide consistent estimates of the comparative risk of VTE nor did they account for important known and unknown patient characteristics that could influence prescribing and likely affect the risk. It remains unclear whether the increased VTE risk seen in some of the epidemiologic studies is actually due to use of drospirenone-containing COCs, or due to underlying conditions of the patients to whom these products are prescribed. None of the studies specifically addressed the VTE risk among teenagers although two studies (Sidney et al, 2011 [FDA-funded study]; Seeger et al., 2007) included women as young as 10 years of age.

The background package can be found at the following link: (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM282462.pdf).

In summary:

- With one exception (Lidegaard et al., 2011), most of the studies evaluated only the 3 mg drospirenone product containing 30 ug of ethinyl estradiol (Yasmin), and did not include Beyaz specifically.
- Most studies included women age 15 to 44 years. The FDA-funded study (Sidney et al, 2011) and the i3 Ingenix study (Seeger et al., 2007) included women as young as age 10 years and as old as 55 years (Sidney et al., 2011) or 59 years (Seeger et al., 2007).
- All epidemiologic studies adjusted for age in some way when evaluating relative risk. Most studies matched on age or age group or included age as a covariate in the analytical models, either directly (Dinger et al., 2007, Sidney et al., 2011) or both directly and as a summary propensity score (Seeger et al., 2007).
- In the Sidney study, 53% of Yasmin users were younger than 25 years of age (2.8% aged 10 to 14 years). This compared to 32% of users of the comparator oral products (COMP) who were younger than 25 years of age (2.0% age 10 to 14 years) - http://www.fda.gov/Drugs/DrugSafety/ucm277346.htm.
- When age was considered in the published studies, information was most frequently presented as part of the demographic characteristics of the population studied for all contraceptive products combined. Only the Sidney study provided age-specific incidence rates of VTE per 10,000 women years by product including drospirenone-containing contraceptives. For the age group 10 to 24 years, the incidence rate among new users was 4.8/10,000 for drospirenone-containing product (Yasmin) compared to 3.1/10,000 for a group of comparator contraceptive products.

- Even with tight age adjustment, an age interaction was noted for VTE with the higher relative risk observed in the younger age group [< 35 years of age compared to 35+ years (Sidney et al 2011) and <30 years of age compared to 30+ years (Jick et al 2011]. In these studies, although the incidence of VTE increased with age, when controlling for age and other variables, the relative risk for VTE in younger women using drospirenone-containing contraceptives was higher than in older women. This may raise concerns for young women using drospirenone-containing contraceptives, including Beyaz.
- The age interaction observed in sensitivity analyses by the Boston Collaborative Drug Safety Program (BCDSP) also showed this increased relative risk in young women to be associated with a history of menstrual disorders (Jick et al BMJ 2011;340:d2151doi:10.1136/bmj.d2151).
- Only one published study (Lidegaard et al., 2011) reported VTE risk for drospirenone-containing COC with 20 ug ethinyl estradiol (EE), a product comparable to Beyaz without the levomefolate calcium. Compared to non-users, the relative risks for the 20 mcg EE product was 4.8 (95% CI: 3.1 -7.3), nearly the same for the 30 mcg product which was 4.5 (95% CI: 3.9-5.1). No age breakdown was provided for either product, however, although both relative risk estimates were adjusted for age, year, and level of education.
- In the Sidney study, 4% of the Yasmin users (which was not approved for the acne co-indication at the time of the study) had a code for acne compared to 2% of COMP users (the COMP group included 31% of norgestimate-containing products which was approved for the acne co-indication at the time of the study).
- No epidemiologic studies to date, however, have addressed safety concerns specifically for Beyaz.

At about the same time as the Advisory Committee meeting (November 2011), Rachel Jones from the Guttmacher Institute published a report of non-contraceptive uses of combined oral contraceptives for a nationally representative population of women age 15-44 years (NCHS Survey) *Beyond Birth Control: The Overlooked Benefits of Oral Contraceptive Pills* (http://www.guttmacher.org/pubs/Beyond-Birth-Control.pdf). The information presented in this report is based on an analysis of the 2006–2008 National Survey of Family Growth (NSFG). The NSFG is collected from a nationally representative sample of women age 15-44 years. The NSFG is designed and administered by the National Center for Health Statistics (NCHS) to provide information about factors affecting pregnancy, including sexual activity and contraceptive use. Data were gathered using in-person interviews with 7,356 women aged 15–44 years of age between June 2006 and December 2008. Data are weighted, and the findings are nationally representative. The analysis was restricted to current COC users, defined as women who reported using COCs in the month of the survey. The information from this report was not presented or discussed at the AC but provides the following information on teenagers

- 82% of teens reported use of combined oral contraceptives (COCs) for non-contraceptive reasons
- 33% of teens reported use of COCs only for non-contraceptive reasons
- Among those who have never had sex, 8% reported using the pill only for non-contraceptive reasons

    - Menstrual pain (54%)
    - Menstrual regulation (33%)
    - Acne (30%)
- Although the Jones report referred only to oral contraceptives in general, 17% of the COCs mentioned contained drospirenone (private communication)

5 CONCLUSION

This postmarketing safety evaluation found no unexpected evidence of pediatric safety concerns with Beyaz.

Although many of the epidemiologic studies based on claims data show an increased risk of thromboembolism with drospirenone-containing products evaluated (those containing 30 mcg EE), the studies reviewed did not provide consistent estimates of the comparative risk, nor did they account for important known and unknown patient characteristics that may influence prescribing and likely affect the risk of thromboembolic events. Therefore, it remains unclear whether the increased risk seen in some of the epidemiologic studies is actually due to use of drospirenone-containing birth control pills. The studies, however, demonstrated clearly that the drospirenone-containing contraceptives have had substantial use by women 10 to 24 years of age and the relative risk of VTE appeared higher for women younger than 30 years of age. Adolescents reported using drospirenone-containing oral contraceptives for co-indications other than or in addition to contraception, an observation supported by this case series as well. These studies, however, provide no specific information on the safety of Beyaz's use among adolescents although it is likely that Beyaz shares the same potential safety risks as other drospirenone-containing oral contraceptives. Therefore Beyaz's label, along with all other drospirenone-containing oral contraceptives, has recently been updated to included information on the possible increased VTE risk conveyed by these epidemiologic studies.

6 RECOMMENDATIONS

DPV I will continue pharmacovigilance activities associated with Beyaz. DEPI-II continues to explore ways to better understand the possible increased risk for VTE associated with all drospirenone-containing products, including Beyaz, in women of all ages.

7 REFERENCES

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Seeger J, Loughlin J, Eng P, Clifford C, Cutone J, Walker A. 2007. Risk of thromboembolism in women taking ethinylestradiol /drospirenone and other oral contraceptives. Obstet Gynecol;110(3): 587-93.

Sidney S and FDA Office of Surveillance and Epidemiology. 2011. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

8 APPENDICES

8.1 APPENDIX A. STANDARD SEARCHES

A. Adults (18 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-17 yrs ONLY
   1. Same as above 1-3

8.2 APPENDIX B. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.3 APPENDIX C. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS

	ISR number	Case number	Manufacturer Control number	FDA received date	Report Type	Age	Reported Outcome	Event date	Reported Preferred Terms (PT) or adverse event terms
1	7352550	7871849	CTU 446926	8-Mar-11	Direct	17	LT, HO	26-Jan-11	PULMONARY EMBOLISM,FALL,CORONARY ARTERY THROMBOSIS
2	7967251	8281596	US-BAYER-2011-115031	9-Dec-11	Expedited (15-Day)	14	HO	7-Nov-11	RETINAL VEIN THROMBOSIS,RASH
3	8121107	8249398	US-BAYER-2011-109349	17-Nov-11	Periodic	16	HO	unknown	CHEST PAIN,DYSPNOEA,SYNCOPE,HEAD INJURY,PULMONARY EMBOLISM
4	7911637	8242758	US-FDA-7911637	14-Nov-11	Direct	16	HO	9-Nov-11	PULMONARY EMBOLISM
5	7843803	7098233	US-BAYER-200924033NA	27-Aug-09	Expedited (15-Day)	17	OT	1-Oct-11	SYNCOPE,PALPITATIONS,ASTHENIA,DIARRHOEA,FEELING ABNORMAL,ABDOMINAL DISTENSION,MYDRIASIS,MENORRHAGIA,NO ADVERSE EVENT
6	7527323	7976696	US-BAYER-2011-045486	7-Jun-11	Expedited (15-Day)	17	OT	unknown	PAIN IN EXTREMITY,CARDIAC DISCOMFORT,ANXIETY,MUSCULOSKELETAL PAIN
7	8019157	8198949	US-BAYER-2011-102661	25-Oct-11	Expedited (15-Day)	17	OT	unknown	TOXIC SHOCK SYNDROME,STREPTOCOCCUS TEST POSITIVE
8	8154247	8419034	US-BAYER-2012-016719	21-Feb-12	Expedited (15-Day)	12	OT	17-Mar-11	DEEP VEIN THROMBOSIS,INFERIOR VENA CAVA SYNDROME
9	8143227	8402588	US-BAYER-2012-013387	13-Feb-12	Periodic	16	OT	unknown	EMBOLISM VENOUS

Reported Outcomes: HO=hospitalization; LT=Life Threatening; OT=other serious

8.4 APPENDIX D: NARRATIVE SUMMARIES FOR PEDIATRIC CASES REPORTING THROMBOEMBOLIC EVENTS (N=6)

	ISR number	Case number	Manufacturer Control number	FDA received date	Report Type	Age	Reported Outcome	Event date	Reported Preferred Terms (PT) or adverse event terms
1	7967251	8281596	US-BAYER-2011-115031	9-Dec-11	Expedited (15-Day)	14	HO	7-Nov-11	RETINAL VEIN THROMBOSIS,RASH
Reported Narrative: This report received from a physician on 29-NOV-2011 describes 14-year-old female who received Beyaz and experienced “face breaking out” and venous thromboembolism in the left eye. No information was given on patient's medical history, drug history or concurrent conditions. On 03-AUG-2011 she started Beyaz for menstrual cycle control. Prior exposure to Beyaz was unknown. The physician reported the patient “did not do well” on Beyaz. Her face was “breaking out”. BEYAZ was discontinued on 10-OCT-2011. Patient was prescribed Loestrin on 10-Oct-2011 and was diagnosed with a venous thromboembolism in the left eye 07-Nov-2011 by another practitioner. The patient was hospitalized due to the last mentioned event. No further information was provided.								
2	7352550	7871849	CTU 446926	8-Mar-11	Direct	17	LT, HO	26-Jan-11	PULMONARY EMBOLISM,FALL,CORONARY ARTERY THROMBOSIS
Reported Narrative (from consumer): Taking Beyaz birth control pills for a little over two weeks. Collapsed near death as the blood clot moved from my heart to both lungs. Several doctors stated this is the only factor she has that would cause this event. She was tested every way she could be to determine the cause of blood clots in a perfectly healthy 17-year-old. She does not smoke or have any other contributing factors. No other reason could be found so the doctors told me it was the pills. This could have been a death if the circumstances had been any different.									
3	8121107	8249398	US-BAYER-2011-109349	17-Nov-11	Periodic	16	HO	unknown	CHEST PAIN,DYSPNOEA,SYNCOPE,HEAD INJURY,PULMONARY EMBOLISM
Reported Narrative: This report received from a nurse on 10-NOV-2011 describes a 16-year-old female who experienced a pulmonary embolism during Beyaz treatment. Her medical history included sprained ankle right (X-ray) on 06-Jul-2011 and sinus infection on 08-Jul-2011, and 10 cigarette/day habit. Prior COC exposure includes Ortho Tri Cyclen (08-Feb-2011 to 28-Feb-2011) and Depo Provera (Jul-2009 to 08-Feb-2011). Depo Provera was restarted on 25-Oct-2011. Concomitant medication included Zithromax, Cymbalta, multivitamin, ibuprofen, Ventolin and Zyrtec. She denied alcohol consumption and drug/substance abuse. Family history includes paternal myocardial infarction at age 35 years. On unspecified date(s), the patient started Beyaz and was hospitalized due to a pulmonary embolism. It was not reported whether or not Beyaz was used previously. Event outcome was not reported or whether Beyaz was withdrawn at the time of report.								
4	7911637	8242758	US-FDA-7911637	14-Nov-11	Direct	16	HO	9-Nov-11	PULMONARY EMBOLISM
Reported Narrative: The patient taking Beyaz at home was admitted to the hospital with bilateral pulmonary emboli. No further information was provided.									
5	8154247	8419034	US-BAYER-2012-016719	21-Feb-12	Expedited (15-Day)	12	OT	17-Mar-11	DEEP VEIN THROMBOSIS,INFERIOR VENA CAVA SYNDROME
Reported Narrative (from legal case): This report was received on 15-FEB-2012 from an attorney on behalf of a 12-year-old female plaintiff. This case is medically confirmed. No information given on patient's medical history or medication history. The patient's concurrent condition included polycystic ovarian syndrome, hypothyroidism, obesity, and moderately severe dysmenorrhea. On an unspecified date the patient started Yaz or Beyaz. It was unknown whether Yaz or Beyaz were used previously. On 19-MAR-2011, the patient experienced a bilateral deep vein thrombosis in lower extremities. On an unspecified date the patient experienced an interrupted inferior vena cava. No further information was provided..									
6	8143227	8402588	US-BAYER-2012-013387	13-Feb-12	Periodic	16	OT	Unknown	EMBOLISM VENOUS
Reported Narrative: This report was received from a physician on 07-Feb-2012 and refers to a 16 year-old female patient who received Beyaz or Yaz and experienced a venous thromboembolism (VTE). No information was provided on the patient's medical history, drug history or concurrent conditions. At the time of report the physician was not sure if the patient took Beyaz or Yaz. It was not reported whether BEYAZ or Yaz was used previously. The patient had a VTE shortly after starting the Beyaz or Yaz. No further information was provided.									

8.5 APPENDIX E: NARRATIVE SUMMARIES FOR PEDIATRIC CASES REPORTING OTHER MISCELLANEOUS ADVERSE EVENT (N=3)

	ISR number	Case number	Manufacturer Control number	FDA received date	Report Type	Age	Reported Outcome	Event date	Reported Preferred Terms (PT) or adverse event terms
1	7843803	7098233	US-BAYER-200924033NA	27-Aug-09	Expedited (15-Day)	17	OT	1-Oct-11	SYNCOPE,PALPITATIONS,ASTHENIA,DIARRHOEA,FEELING ABNORMAL,ABDOMINAL DISTENSION,MYDRIASIS,MENORRHAGIA,NO ADVERSE EVENT
Reported Narrative: A consumer's mother reported her 15 year-old daughter experienced bleeding, diarrhea, and abdominal bloating while on Yaz. The patient switched to Beyaz for an unspecified indication and experienced “fainting spells”. At the end of last 2 cycles, the consumer had a “fainting spell” that lasted about 4-5 seconds. She also experienced “heart racing” and was still weak after the last episode. Her eyes were dilated and she was ”just not right”. The consumer was seen in emergency room on 05-Oct-2011 after her last ”fainting spell”. The “blood work” results were unknown and the electrocardiogram was normal. Consumer had a complete blood panel by her provider and had her potassium level checked. The results were pending. She was not currently on any medication. The reporter stated that she was aware of all the lawsuits and legal actions related to these drugs and was considering that. The consumer was 17 years old when she stopped the product due to ”fainting spell”.								
2	7527323	7976696	US-BAYER-2011-045486	7-Jun-11	Expedited (15-Day)	17	OT	unknown	PAIN IN EXTREMITY,CARDIAC DISCOMFORT,ANXIETY,MUSCULOSKELETAL PAIN
Reported Narrative: This report was received from a consumer’s mother on 25-MAY-2011 which refers to a 17-year-old female patient who was prescribed Beyaz and experienced intermittent pain in right shoulder and hand especially the fingers. The patient felt like she having a heart attack and was anxious. No assessment was given. The reporter declined any follow-up.									
3	8019157	8198949	US-BAYER-2011-102661	25-Oct-11	Expedited (15-Day)	17	OT	unknown	TOXIC SHOCK SYNDROME,STREPTOCOCCUS TEST POSITIVE
Reported Narrative: This report was received on 17-Oct-2011 from a physician referring to a 17 year-old female patient who started Beyaz and previously experienced toxic shock symptoms reappeared. Patient had experienced toxic shock symptoms in the past. On an unspecified date patient started Beyaz for contraception. On an unspecified date, after start of Beyaz, toxic shock symptoms reappeared. The patient was not hospitalized and an outcome was not reported. No further details were provided except there was a positive streptococcus (strep) test added.									

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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07/02/2012

RITA P OUELLET-HELLSTROM
07/03/2012

ADRIENNE M ROTHSTEIN
07/05/2012

ETHAN D HAUSMAN
07/05/2012

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